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Association of multicentricity and prognostic factors of papillary microcarcinoma

Importance of multicentric papillary microcarcinoma

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Abstract

Aim: Multicentric presentation of thyroid papillary microcarcinoma (PMC) is a common feature and difficult to predict preoperatively. The aim of this study was to assess the prognostic importance of the multicentric distribution of papillary microcarcinoma.

Material and Methods: A total of 1356 patients who underwent thyroidectomy between 2011 and 2019 were analyzed. Of the 483 (%35.6) patients with papillary thyroid cancer in the final pathology, macro-carcinomas were excluded and 161 (11.9%) patients with only PMC were included in the study. Patients with solitary PMC (Group 1) and multi-centric PMC (Group 2) were compared statistically in terms of prognostic factors such as tumor size, presence of lymphovascular invasion, presence of tumor capsule invasion and extra-thyroidal extension. Thyroglobulin levels and the presence of loco-regional recurrence were monitored during the follow-up period.

Results: Solitary PMC was found in 106 (65.8%) of 161 patients, and multicentric MPC was found in 55 (34.2%) patients. Tumor sizes were compared, and a larger mean tumor size was detected in Group 2 (6.4±2.2 mm vs. 5.6±2.5 mm) ($p<0.05$). Prognostic factors such as the presence of capsule invasion and extra-thyroidal extension were found to be significantly higher in Group 2 (30.9% vs. 16.3% and 12.7% vs. 2.8%, respectively) ($p<0.05$). Extra thyroidal extension was detected at a much higher rate (18.5%) in the subgroup of multicentric patients with bilateral involvement ($p<0.01$). There was no statistical difference between groups in terms of biochemical incomplete response and loco-regional recurrence.

Discussion: Poor prognostic factors such as large tumor size, capsule invasion and extra-thyroidal extension are more common in patients with multicentric PMC, especially in those with bilateral involvement.

Keywords

Papillary Microcarcinoma, Multicentricity, Prognosis, Extra-Thyroidal Extension

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Introduction

Papillary thyroid carcinoma (PTC) is the most common histopathologic type of thyroid cancers [1]. Papillary microcarcinoma (PMC) is defined as papillary tumors less than 1 cm in diameter by the World Health Organization [2]. According to the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of papillary thyroid carcinoma has more than doubled since 1995 [3]. Due to technical improvements, the detection of smaller thyroid tumors (< 1 cm) by ultrasonography (USG) also contributed to the increase in the incidence of thyroid cancer [4]. Although the widespread use of fine-needle aspiration biopsy (FNAB) has improved the accuracy of preoperative diagnosis of PMC, the majority of PMCs are still detected incidentally in surgical specimens as a result of final pathological evaluation [5]. Patients with PMC usually have an excellent prognosis, but some of the patients may show aggressive behavior, such as loco-regional recurrence, distant metastasis, and death in 0.6% of cases [6,7]. The management of solitary PMCs varies from active surveillance to lobectomy/total thyroidectomy. On the other hand, multicentric PMCs may require total thyroidectomy with or without RAI treatment [8]. PMC has a wide spectrum of treatment options because it is difficult to predict the course of the disease. Higher recurrence rates have been reported to be associated with lymph node metastases, extra-thyroidal extension, and multicentric involvement [9]. The multicentricity of PMC ranges from 9.2 to 32%, and the presence of contralateral disease ranges from 8.1 to 25.6% [10]. Multicentric involvement of PMC in one thyroid lobe has a significant risk for the presence of contralateral PMC focuses. Multicentricity has been reported to be a risk factor for lymph node metastasis and increased cancer recurrence [11].

The aim of this study was to evaluate the association between multicentricity and poor prognostic factors in patients with PMC.

Material and Methods

Patients who underwent lobectomy or total thyroidectomy with or without central lymph node dissection between 2011 and 2019 at the General Surgery Clinic of Istanbul Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin city Hospital were included in the study. Patients underwent thyroidectomy due to thyroid cancer or suspected thyroid cancer, thyrotoxicosis, or compression symptoms such as dysphonia, dysphagia, or dyspnea. Patients with solitary or multicentric papillary microcarcinoma (<10 mm) among patients with papillary thyroid cancer according to the pathology report were included in the study, while patients with macro-carcinoma (>10 mm) were excluded from the study. Patients with a family history of thyroid carcinoma and/or radiation exposure were excluded from the study.

Patients with PMC were also divided into two groups: solitary PMC and multicentric PMC. Solitary PMC patients were classified as “Group 1”, while multicentric PMC patients were classified as “Group 2”.

Solitary and multicentric PMC patients were statistically compared in terms of demographic data, and clinical findings such as nodule status, hormonal status, presence of thyroiditis and tumor size. The presence of lymphovascular invasion (LVI), tumor capsule invasion, extrathyroidal extension, and lymph node metastasis ratios were detected according to pathological evaluation and compared between groups. Also, whether the tumor diagnosis was detected preoperatively by FNAB or incidentally after surgery was compared between groups. During the follow-up period, biochemical incomplete response (Suppressed thyroglobulin >1 ng/ml) and loco-regional recurrence rates, as well as mortality rates were determined by monitoring serum suppressed thyroglobulin value and neck ultrasonography of the patients.

This retrospective research was approved by the local ethics committee on 12.07.2023 with the decision No. 2023/0432. Informed consent was obtained from each study participant.

Results are expressed as mean ± standard deviation. SPSS 20.0 (SPPS Inc., Chicago, IL, USA) was used for the statistical analysis. The Mann-Whitney U test, Chi-square test, and Kruskal-Wallis test were used to for statistical analysis. A p-value <0.05 was considered statistically significant.

Results

The study included 1356 patients who underwent thyroidectomy between 2011 and 2019. Papillary cancer was detected in 483 (35.6%) patients. Among papillary cancer patients, those with a tumor >10 mm were excluded, and 161 (33.3%) patients with PMC (<10 mm) were included in the study. Of the patients, 133 (82.6%) were female and 28 (17.4%) were male, with a mean age of 47.2 ± 12.9 years. According to the nodule status, 125 (77.6%) patients had multinodular goiter and 36 (22.4%) patients had nodular goiter. Hyperthyroidism was detected in 14 (8.7%) of the patients, while 147 (91.3%) patients had euthyroid status preoperatively. While the diagnosis of papillary cancer was made preoperatively with FNAB in 86 (53.4%) patients, PMC was detected incidentally in 75 (46.6%) patients. The presence of thyroiditis in extra-nodular thyroid tissue was detected in 58 (36.1%) patients. The mean tumor size of the patients was 5.9 ± 2.4 mm. Thyroid capsule invasion was detected in 34 (21.1%) patients, lymphovascular invasion in 8 (4.9%) patients, and extrathyroidal invasion in 10 (6.2%) patients. Central lymph node dissection was performed in 16 (9.9%) patients, and lymph node metastasis was detected in only 4 (2.5%) of them (Table 1).

During the mean follow-up period of 62 months, biochemical incomplete response was detected in 17 (%10.6) patients, loco-regional recurrence was observed in 2 (%1.2) patients, and mortality was observed in 2 patients due to non-disease-related. In 7 of 17 patients with an incomplete biochemical response, millimetric residual thyroid tissue was identified in the ultrasonography examination, lymph node metastasis was detected in 2 patients, and no pathological findings were found in 8 patients. When the index operation reports of patients with loco-regional recurrence were examined, it was found that metastatic lymph nodes were dissected in the central region in the first operation in one of the patients, and the primary tumor pathology of the other patient was poorly differentiated carcinoma. No disease-related mortality was detected in any of the patients during the follow-up period (Table 1). Solitary PMC (Group-1) was found in 106 (65.8%) of 161 patients, and multicentric PMC (Group-2) was detected in 55 (34.2%)

patients. While multicentric distribution was located in a single lobe in 28 (50.1%) patients, bilateral involvement was detected in 27 (49.9%) patients. There was no difference between the groups in terms of demographic data such as age and gender. Likewise, no difference was found between the two groups in terms of nodule status, presence of thyrotoxicosis, and thyroiditis (Table 2).

Patient groups were compared in terms of tumor size; we detected that tumor sizes were statistically significantly larger in Group 2 (6.4±2.2 mm vs. 5.6±2.5 mm) (p<0.05). We compared the groups according to tumor diagnostic methods, whether the tumor was detected by suspicious findings on preoperative USG and FNAB, or by postoperative pathological evaluation. It was observed that the preoperative diagnosis rate was statistically higher in the multicentric group. Thirty-seven (67.3%) of the patients were diagnosed with FNAB preoperatively in the multicentric group, while it was diagnosed in 49 (46.2%) solitary PMC cases (p:0.011) (Table 2). Our study reveals that 43.1% of PMCs diagnosed by preoperative USG were multicentric.

In a subgroup analysis, patients with multicentric tumors were compared based on whether the tumor distribution was unilateral or bilateral. It was detected that the mean tumor size was statistically significantly higher in patients with bilateral involvement (5.9±2.4 mm. vs. 7.1±1.8 mm) (p<0.01) (Table 2).

The presence of capsule invasion, which is one of the poor prognostic factors for thyroid cancer, was found to be 30.9% in

Table 1. Descriptive analysis of demographic, clinical and pathological data of patients

	n (%)
Age, mean±SD	47.2±12.9
Gender	
-Male	28 (17.4%)
-Female	133 (82.6%)
Preoperative nodule status	
-Multi-nodular Goiter	125 (77.6%)
-Nodular Goiter	36 (22.4%)
Thyroid function	
-Euthyroidism	147 (91.3%)
-Hyperthyroidism	14 (8.7%)
Presence of thyroiditis	
-Yes	58 (36.1%)
-No	103 (73.9%)
Diagnosis of papillary cancer	
-Preoperative FNAB	86 (53.4%)
-Postoperative incidentally	75 (46.6%)
Tumor size (mm), mean±SD	5.9±2.4
Presence of thyroid capsule invasion	
-Yes	34 (21.1%)
-No	127 (78.9%)
Presence of lymphovascular/perineural invasion	
-Yes	8 (4.9%)
-No	153 (95.1%)
Presence of extra-thyroidal extension	
-Yes	10 (6.2%)
-No	151 (93.8%)
Presence of lymph node metastasis	
-Yes	4 (2.5%)
-No	157 (97.5%)
Biochemical incomplete response	
-Yes	17 (10.6%)
-No	144 (89.4%)
Loco-regional recurrence	
-Yes	2 (1.2%)
-No	159 (98.8%)
Mortalilty	
-Overall	2 (1.2%)
-Disease-related	0 (0)

Table 2. Comparison of demographic, clinical and pathological outcomes of patients between groups

	Group 1 n=106	Group 2 n=55	p
Age, mean±SD	47.5±13.3	46.7±12.1	0.693[a]
Gender			
-Male	19 (17.9%)	9 (16.4%)	0.804[b]
-Female	87 (82.1%)	46 (83.6%)	
Preoperative nodule status			
-Multinodular Goiter	81 (76.4%)	44 (80%)	0.604[b]
-Nodular Goiter	25 (23.6%)	11 (20%)	
Thyroid function			
-Euthyroidism	95 (89.6%)	52 (94.6%)	0.293[b]
-Hyperthyroidism	11 (10.4%)	3 (5.4%)	
Presence of thyroiditis			
-No	68 (64.2%)	35 (63.6%)	0.948[b]
-Yes	38 (35.8%)	20 (36.4%)	
Tumor size (mm)	5.6±2.5	6.4±2.2	0.042*[a]
Tumor size subgroup analysis (mm)			
-Unilateral soliter	-	6.4±2.2	0.028*[c]
-Unilateral multicentric	5.9±2.4	-	
-Bilateral multicentric	7.1±1.8	-	
Diagnosis of papillary cancer			
-Preoperative FNAB	49 (46.2%)	37 (67.3%)	0.011*[b]
-Postoperative incidentally	57 (53.8%)	18 (32.7%)	
Presence of capsule invasion			
-Yes	17 (16.3%)	17 (30.9%)	0.015*[b]
-No	89 (83.7%)	38 (59.1%)	
Presence of lymphovascular/perineural invasion			
-No	100 (94.3%)	53 (96.4%)	0.575[b]
-Yes	6 (5.7%)	2 (3.6%)	
Extra-thyroidal extension			
-No	103 (97.2%)	48 (87.3%)	0.013*[b]
-Yes	3 (2.8%)	7 (12.7%)	
Lymph node metastasis			
-Yes	2 (1.8%)	2 (3.6%)	0.886[b]
-No	104 (98.2%)	53 (96.4%)	
Biochemical incomplete response			
-Yes	9 (5.6%)	8 (14.5%)	0.235[b]
-No	97 (94.4%)	47 85.5%)	
Loco-regional recurrence			
-Yes	2 (1.8%)	0 (0%)	0.547[d]
-No	104 (98.2%)	55 (100%)	
Disease-related mortality			
-Yes	0 (0%)	0 (0%)	null
-No	106 (100%)	55 (100%)	

a Mann-Whitney U test, b Chi-square test, c Kruskal-Wallis test, d Fisher's exact test
*p<0.05.

Group 2, while it was 16.3% in Group 1. The presence of capsule invasion was statistically significantly higher in patients with multicentric PMC (p:0.015). Extrathyroidal extension is accepted as another poor prognostic factor for thyroid cancer, and was also found to be significantly higher in Group 2 (12.7% vs. 2.8%) (p:0.013). Moreover, the presence of extrathyroidal extension increased up to 18.5% in the patients with bilateral multicentric involvement of PMC (p<0.01).

Lymph node metastases were detected in 2 of 8 patients in each group who underwent central lymph node dissection by detecting suspicious lymph nodes on USG or preoperatively. There was no statistical difference between the groups in lymph node metastases (p: 0.886) (Table 2).

Although incomplete biochemical response was detected more in Group 2, there was no statistically significant difference (%14.5 vs. %5.6). While both loco-regional recurrences were detected in Group 1, no statistically significant difference was found.

Discussion

Papillary cancer is the most common type of thyroid cancer, and the Surveillance, Epidemiology and End Results (SEER) database shows that thyroid cancer incidence has more than doubled over the past 2-3 decades [3]. It has been stated that the increase in the incidence of thyroid cancer is mainly due to PMCs [1,12,13], defined by the World Health Organization as thyroid cancer less than 10 mm in diameter [2]. PMCs constitute up to 42.8% of papillary thyroid cancer patients in studies with large case series [14,15].

According to the literature, multicentricity and other poor prognostic features are less common in PMC patients than in PTC patients [15]. Multicentric distribution of PMC is an important situation for surgeons and clinicians, as it may require completion of thyroidectomy after lobectomy [7]. In addition, there are publications in the literature that multicentricity is a poor prognostic factor for papillary thyroid cancers. According to the ATA guideline, if multicentricity is accompanied by extrathyroidal extension in PMC patients, the risk score of patients is elevated to the "intermediate risk group" [7,16].

USG is the most effective imaging method to detect thyroid carcinomas. Its diagnostic accuracy increases if the tumor has microcalcification, border irregularity, extrathyroidal extension, and/or lateral lymph node metastases, while the diagnostic value of USG decreases in case of smaller tumor size [7]. Lu C. et al. stated that USG evaluation is not sensitive enough to detect multicentric PTC [17]. However, in this study, we revealed that the rate of papillary cancer diagnosis by preoperative USG was higher in multicentric PMC patients. Moreover, this study revealed that 43.1% of PMCs diagnosed preoperatively by USG were multicentric. We think that this is due to the larger mean tumor size in the multicentric PMC group compared to solitary PMC patients.

As tumor size increases, the multicentric distribution of PMCs and even the bilateral involvement rates increase. Accordingly, the need for completion of thyroidectomy may be higher in this patient group.

Some studies have stated that multicentric PTC occurs at older ages [16], but in our study, a statistically significant difference was not detected between the groups in terms of age in PMC patients.

Lin et al. [16] stated that the rate of central lymph nodes metastasis was higher in multicentric PMC patients compared with solitary PMC group (20.6% vs. 13.0%, respectively, p:0.001). Loco-regional recurrence rates were also found to be higher in multicentric PMCs (15.9% vs. 5.6%, p<0.05) in the same study. In this study, no statistically significant difference was found in terms of central lymph node metastasis in multicentric and solitary PMC cases.

The presence of LVI is accepted as an independent risk factor for loco-regional recurrence, lymph node metastasis and disease-free survival [18,19]. Kim et al. [20] stated that LVI was found in 33% of PTC patients. Uludağ et al. [15] detected LVI in 14.2% of PMC patients. In this study, LVI was found in 5.7% of multicentric PMC patients versus 3.6% of solitary PMC patients. There was no statistical difference between the groups.

Other poor prognostic factors for PTC patients are the presence of extrathyroidal extension (ETE) and/or capsule invasion. The presence of ETE in PMC patients has been reported in the literature at rates ranging from 2 to 21% [7,15]. In this study, ETE occurred in 12.7% of multicentric PMC patients, while 2.8% of solitary PMC patients had ETE, and the difference between groups was statistically significant. The presence of capsular invasion was found to be 30.9% and 16.3% between multicentric and solitary PMC groups, respectively, with a statistically significant difference.

Lin et al. [16] found that the loco-regional recurrence rate was 9.5% in multicentric cases and 5.6% in solitary cases in the thyroid papillary cancer population that they followed for about 8 years, but they did not detect a statistically significant difference. On the other hand, Zhang et al. [21] found a significant increase in the rates of lateral and cervical lymph node metastasis in the case of multicentric thyroid papillary cancers after 10 years of follow-up. Grodski et al. evaluated PMC patients in their study and detected that the overall recurrence rate was 3.5% with a median time to recurrence of 10.3 years. The majority of recurrences were loco-regional with distant recurrence occurring in 0.6% [9]. In our study, we detected loco-regional recurrence in only two patients (1.2%) with solitary PMC in approximately 5 years of follow-up.

Current guidelines recommend completion of thyroidectomy in cases of multicentric PMC that have undergone lobectomy [6,22]. Our study also supports the necessity of completing thyroidectomy in this patient group.

Conclusion

This study is important because it contains a homogeneous group of 161 patients with only micropapillary cancer, thus we can more clearly reveal the prognostic effect of multicentricity in PMC. In conclusion, this study revealed that tumor size is a significant factor in the occurrence of multicentric and bilateral involvement of PMC. Multicentricity increases the rate of poor prognostic factors such as the presence of capsule invasion, the presence of LVI and the presence of ETE in PMC patients. However, there was no difference detected between multicentric or solitary PMC in terms of either biochemical incomplete response or loco-regional recurrence.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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